REMARKS/ARGUMENTS

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 9, 10, 12, 14-18, and 20-28 are now in the case. Claim 9 has been amended. No new matter has been added.

Claim 9 has been amended for reasons of clarity. No change in scope is intended.

The specification is objected to as containing "a drawing and a brief description of the drawing containing amino acid residue not properly identifying with a SEQ ID number."

This objection is traversed in part and overcome in part. Applicant's specification includes a single drawing. The description of the drawing at page 5 of the specification includes the SEQ ID number for each of the two illustrated sequences. Thus, this section of the specification is believed to be in accordance with the rules and not to require amendment. Applicant is submitting herewith a replacement drawing sheet that has been amended to include these SEQ ID numbers. No new matter has been added. Reconsideration and withdrawal of the objection are requested.

Claims 20, 21, 24, and 25 are objected to as allegedly being in improper dependent form for failing to further limit the subject matter of a previous claim. The Office believes that claims 20 and 21 are broader than the claim limitations of claim 9. The Office states, "Claim 9 sets forth a protein with only residues 6 through 56 encoded by the segment contained in the cultured cell of claim 17." The Office did not provide a specific basis for the objection as applied to claims 24 and 25.

Applicant respectfully traverses this objection. Amended claim 9 recites that the encoded protein is from 51 to 81 amino acids in length and comprises a sequence of amino acid residues as shown in SEQ ID NO:2 from residue 6 through residue 56. In view of the term "comprising" in claim 9, the recited protein includes residues 6 through 56 of SEQ ID NO:2 (51 amino acid residues), but may contain additional residues at the amino and/or carboxyl termini, up to a total length of 81 amino acid residues. Dependent claim 20 recites that the protein comprises residues 1-59 of SEQ ID NO:2. This recitation, which includes five additional residues (i.e., residues 1-5 of SEQ ID NO:2) at the amino terminus of the protein, further limits the protein recited in claim 9. Dependent claim 21 recites that the protein "consists of residues 1-59 of SEQ ID NO:2." Thus, claim 21 further limits the protein recited in claim 9 by specifying five additional residues of SEQ ID NO:2 at the amino terminus and, through recititation of "consisting", limiting the length of the protein. Claims 24 and 25 contain the same limitations as claims 20 and 21, respectively, and thus further limit claim 17 from which they depend. Reconsideration and withdrawal of this objection are requested.

Claims 9, 10, 12, 14-18, and 20-28 stand rejected under 35 USC § 112, first paragraph. The Office believes that the claims fail to comply with the enablement requirement. The Office further believes that the specification only provides enabling disclosure of the production of the Kunitz domain "within the full-length protein", which Applicant understands to mean residues 1-59 of SEQ ID NO:2. According to the Office, "The peptide produced from the polynucleotide segment has the high probability of not maintaining the biological activity or structural specificity of zKun6 polypeptides." Lederman et al., Li et al., and Ngo et al. are cited in support of the rejection.

Applicant respectfully traverses this rejection. As discussed in more detail below, the Lederman, Li, and Ngo references do not support the rejection. The Lederman et al. disclosure is limited to antibody-binding properties of CD4. CD4 is disclosed to be "a relatively non-polymorphic" protein (page 1171, Abstract). The Li et al. disclosure is limited to structure-function relationships in β-endorphin. Li et al. disclose that "the entire β-EP molecule is necessary for full analgesic potency" (page 3211, left column). Ngo et al. is directed to computational prediction of protein folding. None of these disclosures contains any teaching directed to Kunitz inhibitors. As disclosed by Applicant at page 2 of the specification, Kunitz domains, which commonly are components of much larger proteins, retain their inhibitory activity when prepared in isolated form. Thus, Kunitz inhibitors are clearly distinguishable from the β-endorphin of Li et al. Furthermore, in contrast to CD4 and β-endorphin, Kunitz inhibitors are know in the art to be highly polymorphic and tolerant of amino acid substitutions. For example, Lazarus et al. (US Pat. No. 5,795,954; of record) disclose a polypeptide comprising a Kunitz-type serine protease inhibitor domain wherein the amino and carboxyl termini are variable in both length and composition, and the internal residues can be varied according to defined parameters. Certain regions of the polypeptide (e.g., the R_2 region; see claim 1) are extremely maleable. Markland et al. (US Pat. No. 5,795,865; of record) disclose that Kunitz domains contain at least 51 amino acids and up to about 61 amino acids (column 5, lines 15-17). Markland et al. define a Kunitz domain, for purposes of their invention, as a sequence that can be aligned with that of Table 14 with three or fewer mismatches (column 5, lines 21-24). The sequence of Table 14 (column 21) is itself highly variable; of 58 residues shown, only 17 are defined at all, and 8 of those 17 can be selected from groups of 2 or 3 residues. Dennis et al. (US Pat. No. 5,880,256; of record) disclose Kunitz-type serine protease inhibitors of from 46 to 58 amino acid residues having extensive sequence heterogeneity. See, for example, claim 1. Wagner et al. (*Biochem. Biophys. Res. Comm.* 186:1138-1145, 1992; copy enclosed) disclose that the 57 amino acid Kunitz domain of protease nexin-2 (or AβPP) can be produced as a 61 amino acid polypeptide that retains potent inhibitory activity similar to

that of the 751-residue native protease. Sinha et al. (*J. Biol. Chem.* 265:8983-8985, 1990; copy enclosed) produced the Kunitz domain of AβPP as a 194-residue fusion protein. The authors report that the fusion protein was active as a trypsin inhibitor. Petersen et al. (*Eur. J. Biochem.* 235:310-316, 1996; copy enclosed) disclose that the isolated first and second Kunitz domains of tissue-factor-pathway inhibitor exhibit protease inhibition activity. Clearly, the disclosures of Lederman et al., Li et al., and Ngo et al. teach nothing about Kunitz inhibitors, which are known in the art to be highly tolerant of amino acid sequence variation and retain their activity as isolated domains and as components of larger proteins (both naturally occuring proteins and engineered fusion proteins).

As disclosed in Applicant's specification at page 10, SEQ ID NO:2 comprises a Kunitz domain bounded by cysteine residues at positions 6 and 56. In view of the known permissible variation in the sequences of Kunitz domains and proteins containing them, one skilled in the art would reasonably expect that the claimed proteins of from 51 to 81 amino acid residues in length comprising residues 6 through 56 of SEQ ID NO:2 would have biological activity or structural specificity characteristic of Kunitz-type protease inhibitors.

For the reasons discussed above, Applicant requests that the rejection under 35 USC § 112, first paragraph be reconsidered and withdrawn.

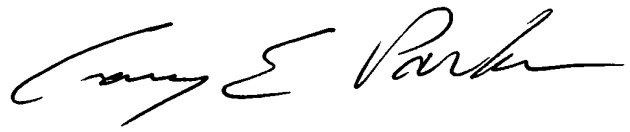
Claims 9, 10, 12, 14-18, and 20-28 stand rejected under 35 USC § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More specifically, the Office states, "Claims 9, 14, 20, 21, and 23-25 are believed to be vague and indefinite in the recitation 'a DNA segment encoding a protein of from 51 to 81 amino acid residues comprising a sequence of amino acid sequences as shown in SEQ ID NO:2 from residue 6 through 56'."

Applicant respectfully submits that the claims as filed fulfill the requirements of § 112, second paragraph. A protein of from 51 to 81 amino acid residues can comprise a sequence of amino acid residues as shown in SEQ ID NO:2 from residue 6 through residue 56. Residues 6 through 56 define a 51-residue polypeptide sequence, which can be contained in (comprised by) a protein of from 51 to 81 amino acid residues. Nonetheless, Applicant has amended claim 9 to more explicitly recite that the protein is from 51 to 81 amino acids in length and that it comprises a sequence of amino acid residues as shown in SEQ ID NO:2 from residue 6 through residue 56. Reconsideration and withdrawal of the rejection are requested.

Applicant believes that each objection and rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for

any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,



Gary E. Parker
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Enclosures:

Amendment Fee Transmittal (in duplicate)
Petition and Fee for Extension of Time (in duplicate)
3 References
Replacement Sheet
Postcard

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